IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) : Richard Hochberg
SERIAL NO. : 10/676,287
FILED : October 1, 2003
FOR : **11β-Short Chain Substituted Estradiol Analogs and Their Use in the Treatment of Menopausal Symptoms and Estrogen Sensitive Cancer**
GROUP ART UNIT : ~~1617~~ 1618
Examiner : BADIO, Barbara P.

MailDrop: Amendment
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Declaration of Dr. Richard Hochberg

I, Richard Hochberg declare as follows:

1. I reference my declaration of May 2, 2007 which was previously filed in the present application with respect to my relationship to the present invention, my scientific background, and my experience. A copy of that earlier filed declaration is attached for the convenience of the Examiner.

2. I have reviewed the Examiner's office action dated January 6, 2010 in the above-referenced application. I understand that in that office action the Examiner rejects previously pending claims 39-56 an 65-73 as being obvious over van den Broek, et al., US patent no. 3,972,906, ("van den Broek") for the reasons which are presented in the January, 2010 office action in point 7. on pages 4-6. I also understand that the Examiner has further rejected previously pending claims 39-56 and 65-73 as being obvious over van den Broek, in view of Cameron, et al., U.S. Patent publication 2001/0025051 ("Cameron"), Palkowitz, U.S. 6,268,906 ("Palkowitz") and Bodor, et al., US. Patent no. 4,617,298 ("Bodor") for the reasons which are stated in point 8. on pages 6-9 of the January, 2010 office action. After review of the office action and the references which are cited therein, I believe that my invention is non-obvious over the teachings of van den Broek alone or van den Broek, in view of Cameron, Palkowitz and Bodor.

3. The present invention, as claimed in claims 39-75 is directed to methods for treating the symptomology of menopause and reducing the likelihood of an estrogen-sensitive cancer in a patient (claims 39-47); a method of treating a patient suffering from an estrogen-sensitive cancer (claims 48-56); a method of reducing the likelihood of a recurrence of breast cancer in a patient (claims 57-64) and a method of treating the symptomology of menopause and estrogen-sensitive cancer in a patient, each of the methods comprising administering to a patient an effective amount of a selective estrogen receptor modulator (SERM) according to the claimed structure. Contrary to the Examiner's view, I believe that the present invention is non-obvious over the prior art teachings.

4. The gist of my invention is the discovery that the compounds as set forth in the claims exhibit unexpected activity as selective estrogen receptor modulators (SERM), an activity which is completely distinguishable from estrogen agonist activity. By this, I mean that the compounds as claimed in the presently pending method claims exhibit biological activity as ***inhibitors*** of certain estrogen receptors (e.g., in the vagina, uterus, breasts and brain), and as ***agonists*** of certain other estrogen receptors (e.g., in liver tissue to reduce plasma lipids and in bone tissue to stimulate bone). The resulting compounds which exhibit this unexpected activity are advantageously used as SERMs for the treatment of the symptomology of menopause related to bone loss associated with osteoporosis, elevated cholesterol and elevated low-density lipoproteins, for the treatment of estrogen-sensitive cancers and the inhibition (reducing the likelihood) of the occurrence of an estrogen-sensitive cancer or recurrence of breast cancer in a patient (because the compounds are antagonists in tissue susceptible to estrogen-sensitive cancer).

5. Contrary to the Examiner's office action, the prior art cited does not teach or suggest the biological activity or methods of use of the compounds which are claimed. The primary reference relied upon by the Examiner is van den Broek. Van den Broek is a patent reference which discloses a larger number of compounds and proposes, but does

not exemplify, any biological activity. There are no examples in van den Broek which are directed to the compounds of my invention and there are no examples whatsoever which test or present the biological activity of any compound, including the compounds which are presented in the present application.

6. The only compounds which van den Broek specifically discloses which are related to the compounds used in my invention are those which have a methoxymethyl group at the 11 position of estradiol. Van den Broek does not exemplify any biological activity associated with those compounds, but does state that those compounds exhibit estrogenic (agonist) activity (see column 2, lines 28-48 of van den Broek). The experiments which are presented on pages 22-25 (see Tables 1 and 2 on pages 23 and 24) of the present application confirm van den Broek's statement that the 11β-methoxymethyl-17α-ethinyl estradiol and 11β-chloromethyl-17α-ethinyl estradiol derivatives exhibit estrogenic agonist activity. Van den Broek does not specifically disclose nor exemplify any compound used in the present invention, which relate to the use of 11β-substituted estradiol compounds which have a chain-length at the 11 position of at least 5 non-hydrogen atoms. These compounds, which are presented in the present claims, exhibit SERM activity and are anti-estrogenic in the uterus, breast, vagina and brain. In contrast, the disclosed van den Broek estradiol compounds are estrogen agonists. Van den Broek does not disclose or suggest SERM activity or the desirability of SERM activity.

7. For the reasons discussed in my previous declaration, I do not believe that van den Broek teaches or suggests compounds which are used in the present invention as estrogen agonist compounds. In fact, my invention is based upon the fact that the compounds which are presently claimed are not estrogen agonists, but show unexpected selective estrogenic receptor antagonism (SERM) activity and are anti-estrogenic in the uterus, vagina, breast and brain. In view of the van den Broek teachings of the desirability of estrogen agonists, the compounds used in the present invention, which exhibit anti-estrogen activity, would not be considered useful by one of ordinary skill in the art. Instead, the present compounds, which are not disclosed in van den Broek, even

if made, would simply be discarded as anti-estrogenic compounds, in complete variance with the teachings of van den Broek and the desirability of obtaining compounds with estrogenic *agonist* activity. In short, the presently used compounds are not specifically taught or exemplified by van den Broek, nor is SERM activity associated with any compounds disclosed or suggested in van den Broek.

8. The Examiner contends that estrogen agonists such as are disclosed by van den Broek are useful to treat estrogen-sensitive cancers and menopause. That characterization is actually incorrect. Estrogen agonists may be useful to treat menopause, especially symptomology associated with the vagina and uterus (e.g. dry vagina, but their use is associated with substantially increased risk and exacerbation of estrogen-sensitive cancer, a contraindication. .

9. The Examiner also contends that the presently claimed compounds are taught by van den Broek and as such, would be used in methods according to the present invention. That characterization of van den Broek is actually inaccurate. In van den Broek, there is no disclosure or suggestion of SERM activity or that any compound in van den Broek exhibits SERM activity. The compounds according to the present invention are not specifically mentioned by van den Broek and there is no motivation in van den Broek to make the compounds of the present invention. In fact, one of ordinary skill would not even make most of the compounds according to the present invention, because the person searching for agonist activity as per the teachings of van den Broek would realize that the presently claimed compounds are anti-estrogenic, not estrogen agonists as desired. Thus, motivation to even make the compounds according to the present invention does not exist because the compounds do not exhibit the requisite activity.

10. Notwithstanding the fact that there is no motivation in van den Broek to make the compounds which are claimed in the present invention, there certainly is no motivation to use the compounds in methods according to the present invention, given that van den Broek teaches and suggests estrogenic agonist activity and the present

compounds and methods rely on the unexpected selective anti-estrogenic (SERM) activity of the claimed compounds in the methods of treatment.

11. The claimed methods all make use of the unexpected pharmacological activity (SERM) of the presently claimed compounds which was discovered pursuant to the present invention. Thus, the claimed compounds, which exhibit unexpected SERM activity, are used favorably to treat certain symptoms of menopause (e.g. osteoporosis, elevated low-density lipoprotein and/or elevated cholesterol) while reducing the risk of estrogen-sensitive cancer in the menopausal patient. Estrogen-agonists, like those disclosed and/or suggested by van den Broek, are contraindicated in the treatment of estrogen-sensitive cancers. It is only the discovery of the unexpected SERM activity of the presently claimed compounds which makes them useful for treating or reducing the likelihood of an estrogen-sensitive cancer as presently claimed. Consequently, I believe that my invention as claimed is non-obvious over the teachings of van den Broek.

12. I also understand that the Examiner has further cited Cameron, Palkowitz and Bodor as teaching that the estrogen agonist compounds of van den Broek can be used to treat estrogen-sensitive cancers. Those references, cumulatively, do not teach that the compounds of van den Broek can be used to treat estrogen-sensitive cancers, but instead support the view, as Applicant respectfully contends, that the use of estrogen agonists is contraindicated and should not be used in estrogen-sensitive cancers because estrogens enhance or worsen estrogen-sensitive cancers. Thus, one of ordinary skill are taught away from using the compounds of van den Broek in the present methods, because it would be expected that such compounds, exhibiting estrogen agonist activity, would actually worsen the cancer and expose the menopausal patient to heightened risk of cancer, a result which stands in complete contrast to the present invention.

13. Based upon the foregoing, I believe that my invention is non-obvious over the teachings of van den Broek, alone or in combination with the teachings of Cameron, Palkowitz and Bodor.

14. Separately, I understand that the Examiner has rejected previously pending claim 57 because she does not believe that a person of ordinary skill could understand the invention that is claimed. Claim 57, as amended, is directed to a method for reducing the likelihood of a recurrence of breast cancer in a patient, the method comprising administering an effective amount of a SERM compound as claimed to that patient. I believe that the invention set forth in claim 57 is clear, concise, and that a person of ordinary, reading claim 57 would understand the invention is claimed and can readily practice the invention. As per claim 57, the present compounds can be used to reduce the likelihood of a recurrence of breast cancer in a patient. This method is much like the methods used for the standard SERM compounds, tamoxifen and raloxifene, which are currently used to reduce the recurrence of breast cancer in a patient. The method of claim 57 is actually quite clear and teaches that the presently claimed compounds, which exhibit SERM activity, can be used in a standard method as is well known in the art (as is currently used for tamoxifen and raloxifene) to reduce the likelihood of recurrence of breast cancer in a patient.

15. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: June 10,2010

Richard Hochberg, Ph.D.

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Declaration of Dr. Richard Hochberg

I, Richard Hochberg declare as follows:

1. I am the sole inventor of the subject matter of the above-referenced patent application.

2. I am a citizen of the United States of America.

3. In 1967, I received a Ph.D. in Biochemistry, from Hahnemann Medical College, in Philadelphia, PA. My thesis title was Studies on the 17β-Hydroxysteroid Dehydrogenase of Human Erythrocytes.

4. Since 1985, I have been a Professor of Obstetrics/Gynecology & Reproductive Sciences and of The Comprehensive Cancer Center, Yale University School of Medicine.

5. From 1980-1985, I held the position Associate Professor of Obstetrics and Gynecology and of Molecular Biophysics and Biochemistry, Yale University School of Medicine.

6. From 1979-80, I held the position of Assistant Professor, Department of Biochemistry, College of Physicians and Surgeons, Columbia University, Department of Medicine, Roosevelt Hospital.

7. From 1974-78, I held the position of Assistant Professor, Endocrine Biochemistry Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University.

8. In 1975, I held the position of Acting director, Gonadotrophin Radioimmunoassay Laboratory, Columbia University.

9. From 1967-74, I held the position of Research Associate, International Institute for the Study of Human Reproductive Dept. of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University. My Research Advisor was Dr. Seymour Lieberman.

10. From 1960-62, I held the position of Research Assistant, Department of Biochemistry, Fairleigh Dickinson University, School of Dentistry, Teaneck, New Jersey.

11. I am the recipient of numerous professional and technical awards and honors, including being an Editorial Board Member of *Endocrinology* (1986-1988); an Editorial Board Member of *Steroid s* (19899-1992); Corresponding Editor of Associate Editor of *J. Steroid Biochemistry and Molecular Biology* (1991-1993); an Associate Editor of *Cancer Research* (1991-2001) and the Editor-in-Chief of *Steroids* (1993-present).

12. I am the sole inventor or co-inventor of several patents/applications in the steroid area, including the present application.

13. I have published over 100 papers in peer-reviewed journals with most of the references being directed to studies on the biology, pharmacology and/or chemistry of steroids.

14. I am familiar with the above-referenced patent application and understand that Examiner Badio has maintained her rejection of claims 1-6 and 13-38 as being obvious

over the disclosure of Van den Broeck, U.S. patent no. 3,972,906 ("the 906 patent").

15. There are several reasons why the presently claimed invention would not be obvious from the '906 patent. Van den Broek and his colleagues disclosed a large number of steroid hormones that are substituted at carbon 11. Specifically relevant to the present application are a series of 11β-methoxy ethers, the major example that he discusses is the methoxy methyl ether of 17α-ethynylestradiol. (For the purpose of this discussion, I ignore the ethynyl group, which protects the 17β-hydroxyl and adds to the pharmacokinetics but does not change its action.) The disclosed compound is a very potent estrogen, and '906 patent discloses it and a large number of similar methoxy ethers as useful for treating menopausal symptoms. However, it is unlike the presently claimed compounds.

16. At the time of the '906 patent (filed in 1975), estrogen therapy was used for treating the menopausal symptoms of vaginal dryness and hot flushes. Such estrogens, were obviously, estrogenic and had stimulatory effects on the female estrogen target organs, vagina and uterus. In fact, the most commonly used method for measuring their potency was on the stimulation of uterine weight in immature or ovariectomized rodents See, Emmens, CW "Estrogens". In: Dorfman RI, ed. Methods in Hormone Research. New York: Academic Press Inc.; pages 59-111 (1962).

17. It is clear that estrogen therapy is the menopausal therapy to which the '906 patent refers. First, because this was the only type of therapy that was useful for estrogens in 1975 and second because the eventual owner of the '906 patent assignee (Organon acquired the '906 patent when it purchased the assets of Akzona, the original assignee of the '906 patent) showed that their lead 11β- methyl methoxy compounds stimulate the uterus. See, Jelinkova M, Jelinek J, de VJ, van d, V 1981 A quantitative test for oestrogenic activity using rat endometrium lactate dehydrogenase. Acta Endocrinol (Copenh) 96:389-39 ("Jelinkova"), previously submitted.

18. In Jelinkova, there is no information that they found differences in any of the 11β-methoxy ether analogs that they claim in the patent. However, had they actually

synthesized the vast list of compounds that they claim (from the teachings, they obviously did not) they would have found that the compounds of the present invention did not have the activity they desired and to which the '906 patent refers.

19. Pursuant to the present invention, a large number of 11β-ether analogs of estradiol were synthesized and tested and the results found were both surprising and are completely at odds with the '906 patent. The studies were published in the Journal of Medicinal Chemistry, copy of a paper previously submitted and attached ("the JMedChem paper"). As can be seen in Figure 2a of that publication, the methyl methoxy ether ($-CH_2O-CH_3$) is highly estrogenic as is claimed by the '906 patent, but the slightly longer ethyl ethoxy ether ($-CH_2O- CH_2CH_3$) is less estrogenic and when the 11β-sidechain is lengthened by one more methylene group to the propyl methoxy ether ($-CH_2O- CH_2CH_2CH_3$) of the present invention, it is essentially devoid of estrogenic activity, as is the longer-chained butyl methoxy ether ($-CH_2O- CH_2CH_2CH_2CH_3$). In fact, the latter 2 compounds, instead of being estrogenic, they are in fact, ***antiestrogenic***, an undesirable activity as taught by the '906 patent. These compounds inhibit the stimulatory effect of estradiol (Figure 2b) of the enclosed JMed Chem paper. This assay was performed with human uterine cells in culture, a well known assay of estrogenic potency. See, Littlefield, et al., "A simple and sensitive microtiter plate estrogen bioassay based on stimulation of alkaline phosphatase in Ishikawa cells: Estrogenic action of Δ^5 adrenal steroids." *Endocrinology*, 127:2757-2762 (1990). Had the inventors of the '906 patent synthesized the compounds that they described and tested them in their own assay, they would have found that they did not posses the estrogenic activity that they desired.

20. It is obvious from the '906 patent and the subsequent paper Jelinkova, that the activity of compounds according to the present invention was neither expected nor taught in the '906 patent.

21. Although antiestrogens, the present compounds are useful for treating menopausal symptoms because some antiestrogens (such as the unrelated tamoxifen), that are

antiestrogenic in vagina, uterus, breast, brain, are estrogenic in other tissues such as liver (reducing plasma lipids) and in stimulating bone. See, Jordan, VC, "Chemosuppression of breast cancer with tamoxifen: laboratory evidence and future clinical investigations." *Cancer Invest,* 6:589-595 (1988).

22. These compounds are now termed selective estrogen receptor modulators (SERMs) indicating that their estrogenic effects are tissue selective (for a review see the attached Jordan VC 1998 Designer Estrogens. Scientific American October:61-67). In the present invention, we showed that 11β-substituted estrogens that are antiestrogenic *in vivo* in the uterus are estrogenic in the liver (compare Figures 5a and 5b of the attached JMedChem article). Thus, they are SERMs and unlike the compounds which are described in the '906 patent. These SERMs are therapeutic in menopausal women because they reduce the risk of breast cancer (inhibiting estrogenic effects in breast) while stimulating bone and reduce circulating lipids. The '906 patent was filed at least 12 years before it was known that SERMs existed and had the inventors of the '906 patent synthesized and tested those 11β-methoxy ethers (they clearly did not even do that) that were synthesized and tested pursuant to the present invention, they would not have found the requisite estrogenic activity that the '906 invention requires. In fact, at the time of the '906 patent it would have been counterintuitive to think that antiestrogens would be useful for treatment of the symptoms of menopause.

23. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5/2/2007

Richard Hochberg, Ph.D.